UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/839,194	02/20/1992	KATHERINE GORDON	G0744.70042US07	6108

31904 7590 10/05/2009

GTC BIOTHERAPEUTICS, INC.
C/O WOLF, GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
10/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	07/839,194	GORDON ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-8,11,16,17 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,11,16,17 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/282009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments have been considered but are not found persuasive.

2. The rejection of claims 1, 2, 5-8, 16, 17, 30 and 31 under 35 USC 103(a) is withdrawn in light of Applicant's argument that it is not obvious to combine the references to arrive at the claimed invention.

3. Claims 1, 2, 5-8, 11, 16, 17 and 30-33 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the office action mailed on 12/4/2008.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 6/3/2009 that on page 2 of the instant specification, it is taught that the promoter can be that of a milk serum protein or a casein protein. Applicants continue that examples of milk serum proteins, which include alpha-lactalbumin, are given, for example, on page 4 of the instant specification (lines 6-15).

Applicants continue that it follows that the combination of these passages give support for milk serum protein promoters, such as the alpha-lactalbumin promoter, and not just the milk serum proteins themselves. Applicants continue that the Examiner is respectfully reminded that *in haec verba* support (i.e., literal support) is not required for the disclosure to satisfy the written description requirement, and a term can be supported in the specification through express, implicit or inherent disclosure (citing MPEP 2163(I)(B) and 2163.02). Applicants continue that the above-mentioned passages provide support for the alpha-lactalbumin promoter through express, implicit or inherent disclosure, and the rejected term, therefore, does not constitute new matter.

Applicant continues that the Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in Applicant's disclosure a description of the invention defined by the claims (citing Wertheim, 541 F.2d at 263, 191 USPQ at 97). Applicant concludes that the Examiner has not demonstrated by a preponderance of evidence that one of ordinary skill in the art would not have recognized that the alpha-lactalbumin promoter is described in view of the disclosure of the application as filed.

These arguments are not found persuasive

Response

As the Non-Final rejection dated 12/4/2008 set forth on pg. 3 lines 1-4, the promoter and the protein of alpha-lactalbumin are distinct from each other. Applicants argue that the specification teaches that the promoter can be that of a milk serum protein or a casein protein, however the specification makes no mention to an alpha-lactalbumin promoter (which is nucleic acid) and the specification makes only one mention regarding alpha-lactalbumin, which is

referring to the protein. Contemplating or mentioning the name of a class or genus of proteins i.e. milk serum proteins in know way provides the specific support required by the claims for a promoter for one particular member of milk serum proteins . Proteins and promoters are entirely different molecular entities, one existing as nucleic acid and the other as a protein. Even knowing a protein's complete structure does not provide for that protein's promoter, promoters are defined and characterized from the gene encoding a protein, not the protein itself. Applicant's arguments that following the combination of several passages on different pages of the specification would lead to sufficient support for claim 31 and thus literal support is not required are not persuasive. These teachings in the specification regarding alpha-lactalbumin are drawn entirely to the proteins and their function and not the specific promoters such as alpha-lactalbumin that would be required to drive their expression. Again it is reiterated that the specification only refers to alpha-lactalbumin as an example of a milk serum protein (pg. 4 lines 11-12) and in no way teaches or refers to the promoter of alpha-lactalbumin. Thus for these reasons above and of record the rejection is maintained.

Claims 1, 2, 5-8, 11, 16, 17 and 30-33 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record in the office action mailed on 12/4/2008.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 6/3/2009 that the Examiner has failed to present any evidence, let alone a preponderance of evidence, to demonstrate that a person skilled in the art would not recognize a description of the mammalian milk protein promoters. All that is provided are the Examiner's opinions.

Applicants continue, that the Examiner argues that, except for the WAP promoter, the instant disclosure only provides examples of mammalian milk proteins and not promoters, however Applicants argue this is not the case. Applicants continue that the instant specification clearly describes promoters by specifying that the promoters can be derived from any of a number of examples of mammalian milk proteins. The genus of milk proteins can be divided into subgenera: the milk serum protein promoters (promoters of WAP, alpha-lactalbumin and beta-lactoglobulin) and the casein protein promoters (promoters of alpha, beta, kappa and gamma casein). Applicants continue that the instant specification provides that the promoter can be that of a milk serum protein or a casein protein (See, e.g., page 2 of the instant specification) and that specific examples of milk serum proteins are provided and include WAP, alpha-lactalbumin and beta-lactoglobulin. (See, e.g., page 4, lines 6-15, and page 15, lines 2-10 of the instant specification). Applicants continue that such teachings go beyond the disclosure of only the recited proteins as argued by the Examiner, and that again, *in haec verba* support is not required for the disclosure to satisfy the written description requirement, and a term can be supported in the specification through express, implicit or inherent disclosure. See MPEP 2163(I)(B) and 2163.02. Applicant maintains that the above-mentioned passages provide support for the

promoters of these proteins and is sufficient to convey to one of ordinary skill in the art that the inventors has possession of the genus of mammalian milk protein promoters.

Applicants continue that the Examiner argues that the DNA sequences of the promoters are required. The Examiner cites two cases, Fiers v. Fevel and Amgen v. Chugai to support this alleged requirement. Applicants argue that Fiers v. Fevel and Amgen v. Chugai, however, are easily distinguishable from the facts of the instant case. The gene sequences at issue in these two cited cases were novel gene sequences having no sequence structure known in the art and defined only by their function. Applicants continue that the sequences of mammalian milk protein promoters, however, were known in the art at the time the instant application was filed. Applicants continue that they have provided five references, which exemplify the knowledge in the art at the time the instant application was filed, and which provide the cloned genomic sequence, identifying the 3' end of the 5' regulatory region, identifying the characteristic 5' regulatory structures and provide a significant amount of DNA sequence for the promoter regions of five of the seven types of mammalian milk protein promoters (Applicants cite: Qsaba and Safaya (1984), *Similarity of the nucleotide sequences of rat lactalbumin and chicken lysozyme genes,* Nature, Vol. 308 (Exhibit A); Campbell and Rosen (1984), *Comparison of the whey acid protein genes of the rat and mouse,* Nucleic Acids Research, Vol. 12, No. 22 (Exhibit B); Yu-Lee et al. (1986), *Evolution of the casein multigene family: conserved sequences in the 5' flanking and exon regions,* Nucleic Acids Research, Vol. 14, No. 4 (Exhibit C); Jones et al. (1985), *The Rat Casein Multigene Family: Fine Structure and Evolution of the fl-Casein Gene,* The Journal of Biological Chemistry, Vol. 260, No. 11 (Exhibit D); Yu-Lee and Rosen (1983), *The Rat Casein Multigene Family: I. Fine Structure of the gamm-Casein Gene,* The Journal of

Biological Chemistry, Vol. 258, No. 17 (Exhibit E). Applicants continue that promoter regions for at least two of three types of milk serum proteins were known as were at least three of four types of caseins. Applicants continue that the Examiner is respectfully reminded that information which is well known in the art need not be described in detail in the specification. See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) and MPEP 2163.

Applicants continue to argue that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species (MPEP 2163.05) and that the description of one or more species is representative, and adequately describes the genus, when the evidence indicates ordinary artisans would predict the operability of any of the species of mammalian milk protein promoters based on the representative species (citing In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). Applicants continue that as demonstrated above, the instant specification provides a description of a number of species of the small genus of mammalian milk protein promoters, a large proportion of which was well-characterized and defined in the art at the time of the filing of the instant application. Applicants continue that in addition, the operability of any of the species of mammalian milk protein promoters would have been predicted by one of ordinary skill in the art at the time the instant application was filed based on the disclosure provided.

Applicants continue that at the time the invention was made, many genes encoding milk proteins had been cloned and transcriptional regulatory sequences involved in their expression identified and at least partially characterized, and it was generally understood that milk protein genes might share one or more regulatory elements conferring mammary specific and hormone

controlled expression (See Paragraph 6 of the Third Declaration Under 37 CFR 1.132 of Katherine Gordon). Applicants continue that the milk proteins coordinately expressed in lactating mammary epithelia were presumed to share similar regulatory mechanisms for expression and one skilled in the art, at the time the invention was made, and in light of the disclosure in the application, would have reasonably expected that transcriptional regulatory sequences derived from other members of the class of milk serum proteins would function within the same or similar manner as the WAP regulatory sequences (See Paragraph 7 of Ibid). Applicants continue, therefore, that the disclosure of the species provided in the instant specification adequately describes the genus, as the evidence indicates ordinary artisans would have predicted the operability of any of the species of mammalian milk protein promoters based on Applicant's teachings.

Applicants continue that they are also providing herewith three post-filing references that demonstrate that due to Applicant's invention, those of ordinary skill in the art were able to successfully express genes of interest using promoters of casein proteins and all of the above-mentioned mammalian milk serum proteins in a number of species (e.g., mouse, goat, pig, sheep, rabbit and cattle). See Maga and Murray (1995), *Mammary Gland Expression of Transgenes and the Potential for Altering the Properties of Milk,* Bio/Technology, Vol. 13 (Exhibit K); Clark (1998), *The Mammary Gland as a Bioreactor: Expression, Processing, and Production of Recombinant Proteins,* Vol. 3, No. 3 (Exhibit L); Echelard and Meade (2003), *Protein production in transgenic animals,* Chapter 24, S.C. Makrides (Ed.) *Gene Transfer and Expression in Mammalian Cells* (Exhibit M).

Applicants continue as the Examiner' s opinions are not sufficient to establish by a preponderance of evidence that one of ordinary skill in the art would not recognize a description of mammalian milk protein promoters in the instant application, and have been contradicted with the above arguments and evidence, withdrawal of this rejection is respectfully requested.

Response

Applicant's arguments "that the instant specification clearly describes promoters by specifying that the promoters can be derived from any of a number of examples of mammalian milk proteins" are not persuasive. Possessing a protein does not imply possession of a promoter for said protein. Further there are no disclosed sequences provided in the instant application, neither for a protein sequence or a nucleic acid sequence. Applicants have consistently argued that possession of the protein results in either the possession of the corresponding promoter or that the promoter can be determined from possession of the protein. However, again, this is simply not the case. Promoters are nucleic acids and proteins are encoded by genes made up of nucleic acids, thus they are two distinct and separate molecular entities. Possession of the protein does not amount to possession of the gene promoter as one cannot readily envision its structure given the guidance in the specification. Applicants argue that the Examiner has provided no evidence, only opinion, to demonstrate that a person skilled in the art would not recognize a description of the mammalian milk protein promoters. However, in this instant case evidence is not needed to demonstrate to the ordinary artisan that possession of all milk serum protein promoters is not provided in the instant application. The ordinary artisan would readily conclude based upon the complete lack of any sequences (nucleic acid or amino acid) that no promoters are taught by or possessed by Applicant other than the WAP promoter. The nucleic acid

sequence for milk serum protein promoters is required since the claims encompass any and all milk serum protein promoters and of which only one member of this genus is described, the WAP promoter.

Further Applicants arguments regarding the teachings provided in Exhibits A-E are also not persuasive. The teachings of Campbell and Rosen (1984) discuss the WAP protein gene among rat and mouse, which as discussed in the rejection, Applicant has demonstrated possession of. The work by Jones et al., Yu-Lee (1983) and Yu-Lee (1986) all are related to the casein gene family, either the beta-casein gene or the gamma-casein gene. While the TATA sequence has been identified in both of these genes, neither of these references provide evidence that Applicant was in possession of the promoter sequences for the casein family of proteins. Regarding the teachings of Qasba et al. regarding the alpha-lactalbumin gene, Qasba has also identified the TATA box in this gene, however again, this does not demonstrate that Applicant was in possession of the promoter for any lactalbumin protein. Accordingly, a representative number of species of milk serum protein promoters at the time of filing were not described such that it would be demonstrated to the ordinary artisan that Applicant was in possession of any and all milk serum protein promoters.

Applicants argument that “the disclosure of the species provided in the instant specification adequately describes the genus, as the evidence indicates ordinary artisans would have predicted the operability of any of the species of mammalian milk protein promoters based on Applicant's teachings" is also not persuasive. The only disclosure in the specification regarding mammalian milk protein promoters are their names, no supporting sequence structure that would demonstrate a related or common structure among milk serum protein promoters is

provided in the specification. Further, the art provided by Applicant does not remedy this deficiency in teaching since, other than the WAP promoter, other milk serum protein genes were just being sequenced (at the time of filing) with no corresponding promoter analysis provided to the ordinary artisan that would demonstrate or teach how one promoter sequence may predict or relate to another sequence.

In summary, Applicant has mentioned several milk serum proteins by name, however Applicant has not demonstrated any possession of the nucleic acid sequences that encode these proteins. Possession of a protein does not constitute possession of the corresponding promoter of said protein since by nature, the promoter is made of nucleic acid and the protein of amino acids. At the time of filing as well as today one cannot readily envision the structure of the promoter given the protein sequence. Further, there exists no known scientific method that would allow the ordinary artisan to elucidate the promoter sequence or its structure from a produced protein. Applicant has demonstrated possession of the WAP promoter, however Applicant has not demonstrated possession of all or any other milk serum protein promoter. Further, the specification provides no teachings regarding the common or related structures or sequences of milk serum protein promoters such that the ordinary artisan could elucidate other milk serum protein promoters. Thus for the reasons above and of record the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5-8, 11, 16 and 17 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,727,405 for reasons of record in the office actions mailed on 8/7/2006, 5/2/2007 and 12/4/2008.

Claims 1, 2, 5-8, 11, 16, 17 and 30-33 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 7,045,676 for reasons of record in the office actions mailed on 8/7/2006 and 12/4/2008.

Response to Arguments

Applicants argue in amendment filed 6/3/2009 that when the claims are in otherwise allowable form, Applicant will file a terminal disclaimer at that time. This is not persuasive. A statement of acquiescence over a pending rejection does not overcome the rejection and thus the double patenting rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David A. Montanari
AU 1632
/Valarie Bertoglio/
Primary Examiner, Art Unit 1632